Exhibit 4

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Allergic Fungal Sinusitis

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Allergic fungal sinusitis
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ACAAI Annual Meeting 2002

Objectives:
1. Discuss various forms of fungal sinusitis, with emphasis on the differing clinical presentations.
2. Discuss diagnostic criteria and treatment options for AFS
3. Explain why the team of an allergist, otolaryngologist, pathologist, mycologist and radiologist is essential in the evaluation and management of patients with suspected AFS
4. Identify issues in pathogenesis, diagnosis, treatment and followup that warrant further investigation.

I. Fungal sinusitis

A. First described in the 18th century
- invasive infection
- indolent infection
- mycetoma
- allergic fungal sinusitis (AFS)

B. Allergic fungal sinusitis
- reported as a distinct entity only in the past 20 years.
- most patients are age 10-60 years
- nasal polyposis, chronic sinusitis, and sometimes asthma
- some have concomitant allergic bronchopulmonary mycosis
- long history of rhinitis or asthma
- positive skin tests to multiple inhalant allergens in addition to the fungi
- prevalence in patients requiring surgery for chronic sinusitis estimated at about 6%

II. Etiology, pathogenesis

A. AFS is considered to be a Type I hypersensitivity response to fungi, with both clinical and histological similarities to allergic bronchopulmonary aspergillosis.

B. Because of the association of eosinophilic inflammation, it may be considered a subcategory of chronic eosinophilic hyperplastic sinusitis.

C Most organisms implicated by culture of allergic mucin are in the Deuteromycetes class and the Moniliales order.

D. The prototype organisms in the Moniliaceae are in the genus Aspergillus; these are the same organisms implicated in ABPA. Other Moniliaceae include Penicillium, Gliocladium, Monilia, Cephalosporium, Paecilomyces, and Trichoderma species.

E. The majority of fungi isolated belong to the Dematiaceae family. The fungal genera in this family (which contain melanin in their cell walls) commonly reported in AFS include Dreschlera, Curvularia, and Bipolaris; other genera in this family include Alternaria, Stemphylium, Spondylocladium, Helminthosporium, Cladosporium, and Aureobasidium. Their role in pathogenesis is assumed, but has never been proven.

F. Manning et al. cultured dematiaceous fungi from 16 of 24 AFS patients. *Bipolaris spicifera* was the organism most commonly encountered. Fifteen subjects demonstrated at least one positive in vitro test for specific IgE to the dematiaceous fungi, and 12 were positive to all 3 dematiaceous fungi tested. Five control patients with negative histology and cultures for fungi did not demonstrate fungal specific IgE. In a series of 11 patients at this center meeting the above strict criteria for diagnosis of AFS, 3 were culture positive for *Alternaria alternata* or another Alternaria species, 3 were culture positive for Bipolaris species, 2 to *Curvularia lunata*, and one each to Fusarium species, *Penicillium funicolosum*, and *Cladosporium herbarum*.

G. Many of these are important plant pathogens that are also found in soil and in general aeroallergen sampling.

H. Review of the literature is complicated by use of various fungal classification schemes. The nomenclature used by allergen extract companies is different from that used by mycologists. Fulfilling the diagnostic criterion that patients should have demonstrated IgE-mediated allergy to the organism cultured from allergic mucin is difficult because only a limited number of testing materials is available. For instance, the imperfect state of *Cochliobolus spicifer* may be termed

Bipolaris spicifera or *Drechslera spicifera* by different authors. An extract for diagnostic testing is not commercially available; in previous studies at this center and elsewhere, extracts have been prepared on premises. While allergenic differences between genera might be expected, species differences in allergenicity should be assumed until proven otherwise. Furthermore, many fungal allergens are digestive enzymes, and a single fungal strain may produce differing allergen profiles depending on culture conditions. The available extracts are not standardized, and only a few have characterized allergens. Nonetheless, patients typically demonstrate reactivity to extracts from many different fungi, as well as other inhalants.

I. Presumably, the spores of common environmental fungi enter the sinuses and proliferate, producing fungal specific IgE (and perhaps IgG) responses and ensuing eosinophilic inflammation.

J. Data from this center strongly implicate Aspergillus and Fusarium sp. as major causative agents on the basis of histologic examination of allergic mucin and testing for specific IgE, including recombinant *Aspergillus fumigatus* allergens (McCann, 2002). If these findings hold up prospectively, AFS may even more analogous to ABPA than currently thought.

K. The etiology of ongoing postoperative eosinophilic inflammation has not been determined. Hypotheses are: 1) Fungi remain in the sinuses postoperatively and regrow, driving the continued inflammatory process; 2) Continued exposure to environmental fungi results in postoperatively recolonization if he sinuses; 3) The initial IgE response to fungal allergens results in production of an IgE antibody that also recognizes nonfungal protein(s) present in the sinus cavities.

L. At this center, Chrzanowski demonstrated by IgE immunoblotting that sera from the 11 patients studied recognized an 18 kD protein present in the fungal extracts, perhaps accounting for the clinical observation that patients typically have broad fungal skin test reactivity. A similar molecular weight protein in autologous allergic mucin was recognized by only 4/11 patients in IgE immunoblotting. Unexpectedly, sera from all 11 patients consistently recognized 35-50 kD bands in allergic mucin, corresponding with a band in a fungal extract in only one patient. The identity of these proteins has not been determined, but sera from 2 of 3 arbitrarily selected AFS patients recognized 35-50 kD bands in both allergic mucin and a human epithelial extract. Results of this study suggest that skin test reactivity to a multitude of fungal extracts might be due to a low molecular weight fungal panallergen and raise the question of whether an ongoing IgE response to a human protein accounts for the difficulty in managing patients postoperatively.

III. Diagnosis

A. Presumptive diagnosis is made from history and physical examination, the finding of nasal polyps, and characteristic CT findings. The finding of peripheral eosinophilia, and elevated serum total IgE adds weight to the diagnosis. Preoperative steroid therapy (e.g., for nasal polyposis) may make diagnosis difficult.

B. Diagnosis is confirmed by the finding at surgery of typical brown, peanut-butter-like "allergic mucin", with its characteristic eosinophils, Charcot-Leyden crystals, and fungal hyphae. There must be no evidence of tissue invasion on examination of mucin and mucosa. Culture identification of a fungus, and the finding of specific IgE (by skin testing or in vitro assay) and specific IgG (by gel diffusion or immunoassay) antibodies to fungi further support the diganosis.[10, 11]

C. Minimal diagnostic criteria (Bent and Kuhn)

1. Nasal polyps
2. Characteristic CT findings
3. Allergy (immediate hypersensitivity) by skin testing or specific IgE immunoassay
4. Allergic mucin
5. Positive fungal stain of allergic mucin

D. MCG "strict" research criteria (5 of the following 6 criteria for a "firm" diagnosis)[13]

1. Chronic sinusitis – characteristicCT findings (essential)
2. Allergic mucin with fungal hyphae, eosinophils, and Charcot-Leyden crystals; no tissue invasion (essential)
3. Positive fungal ~~culture~~ of allergic mucin from the sinus
4. Presence of specific IgE

5. Elevated total serum IgE (>150 IU/mL)
6. History and physical examination do not suggest another etiology

E. Mayo clinic case definition (Ponikau 1999)
1. Chronic rhinosinusitis confirmed by CT
2. Presence of allergic mucin (eosinophils and their "degenerated by-products")

IV. Utility of laboratory tests

A. Unlike allergic bronchopulmonary mycosis, serial measurement of serum total IgE has not consistently been of value in predicting clinical exacerbations or monitoring therapy.

B. Levels of eosinophil cationic protein (ECP), a marker of eosinophil activation, are elevated in allergic mucin of nearly all patients and in the serum of some; preliminary data (not yet prospectively confirmed) suggest that mucin ECP level > 7000 μg/L correlates with disease activity in some patients.

V. Evaluation

A. Collaboration essential

B. Initial evaluation
- Detailed medical history and physical examination with special emphasis on rhinosinusitis (how was sinusitis documented?), recurrent infections, pulmonary disease, ASA sensitivity. Details of prior therapy, including antibiotics and immunotherapy
- Allergy testing to braod panel of pollens, dust mites, danders, fungi
- CBC with diff, ESR, chem. Panel, total IgE level
- Upper airway endoscopy
- Sinus CT – notify radiologist that AFS is suspected
- Consider: CXR or chest CT, sinus MRI, spirometry, sweat chloride, CF genotyping, immunoglobulin levels, anergy testing, other screening tests for immunodeficiency

C. At surgery
- Notify pathologist that AFS is suspected; ask pathologist to report gross description or specimen, H&E stains of mucin and mucosa, specifically commenting on presence or absence of tissue invasion, hyphae, eosinophils, Charcot-Leyden crystals. A pathologist expert in the visual identification of fungi in situ in tissues should be asked to review the GMS slide.
- Sample of mucin inoculated into duplicate Sabouraud tubes in the operating room. One tube sent to clinical lab, the other to an expert mycologist.

D. Followup
- Interim history and examination
- Endoscopic staging using Kupferberg-Kuhn criteria
- Consider additional testing

Management

A. Surgical drainage of the affected sinuses. This leaves large antral windows and marsupialized ethmoid sinuses that can be used for endoscopic followup.

B. Kupferberg-Kuhn staging criteria. Sinuses are visualized by rigid endoscopy.
Stage 0: no mucosal edema or allergic mucin
Stage 1: Mucosal edem with or without allergic mucin
Stage 2: Polypoid edema with or without allergic mucin
Stage 3: Sinus polyps with fungal debris/mucin

C. Topical or systemic corticosteroids. Prednisone 40 mg (0.4 – 0.6 mg/kg/day) daily for 4 days, 30 mg (0.3 – 0.4 mg/kg/day) daily for 4 days, 20 mg (0.2 mg/kg/day) daily for one month used postoperatively at this center. Dosage tapered in followup, using Kupfer-berg-Kuhn criteria, keeping sinuses at Stage 0. Dosages less than 15 mg alternate day generally leading to recurrence. There are no clear guidelines for adjusting steroid taper without endoscopic guidance. Corticosteroids given preoperatively may make diagnosis difficult; when possible, this therapy should be withheld until the diagnosis is established.

D. Alternative treatments
- Topical intranasal steroids: Kuhn 2000.

- Antileukotrienes: Schubert 2001
- Immunotherapy: increasing evidence that IT may delay recurrence (Bassichis 2001). Standardized extracts not available, thus dose-ranging studies not possible. No double-blind, placebo-controlled trials.
- Environmental control
- Topical or systemic antifungal agents: literature in conflict
- Anti-IgE, anti-cytokine therapy: untested

E. Long-term remission following surgery, although reported, seems to be rare

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Fungal synonyms from the CBS database

Moniliaceae	**Synonyms**	**Molecular data***
Aspergillus fumigatus	A. fumigatus, var. fumigatus, Fresenius A. fumigatus, var. acolumnaris A. phialiseptus A. anomalus A. cellulosae A. fumigatus, var. ellipticus, Roper & Fennell	Asp f 1-4, Asp f 7, Asp f 9, Asp f 13
Fusarium moniliforme	syn. of F. proliferatum, var. proliferatum syn. of F. verticillioides, (Saccardo) Nirenberg F. celosiae Oospora cephalosporoides F. moniliforme var. anthophilum F. anthophilum F. moniliforme, var. minus F. proliferatum, var. minus	pgA - GenBank beta tubulin - GenBank
Penicillium notatum	syn. of P. chrysogenum, Thom P. notatum, Westling, P. camerunense, P. cyaneofulvum, P. harmonense, P. melagrinum, P. baculatum, P. brunneorubrum, P. chlorophaeum, P. fluorescens, P. griseoroseum, P. roseocitreum	68 kD allergen - GenBank

Dematiaceae	**Synonyms**	**Molecular data***
Alternaria alternata	A. alternata, (Fries:Fries) von Keissler A. tenuis, Nees A. fasciculata, (Cooke & Ellis) Jones & Grout A. mali, Roberts A. rugosa, McAlpine	Alt a 1-2; Alt a 6-7, Alt a 10, Alt a 12
Cladosporium herbarum	C. herbarum, (Persoon:Fries) Link C. entoxylinum C. gramineum	Cla h 2-6
Curvularia lunata	C. lunata, var. lunata (Wakker) Boedijn alternative state of Cochliobolus lunatus C. lunata, var. aeria Malustela aeria Acrothecium lunatum Helminthosporium curvulum	gpd- GenBank (no allergens reported)
Helminthosporium halodes (see E. rostratum)	H. halodes, Drechsler syn. of Exserohilum rostratum Drechslera halodes D. rostrata H. rostratum	(No matches)
Exserohilum rostratum	E. rostratum, (Drechsler) Leonard & Suggs alternative state of Setosphaeria rostrata Helminthosporium leptochloae H. halodes Drechslera halodes H. rostratum D. rostrata	No matches
Bipolaris spicifera	B. spicifera, (Bainier) Subramanian alternative state of Cochliobolus spiciferus Curvularia spicifera, (Bainier) Boedijn Drechslera spicifera, (Bainier) von Arx D. tetramera, (McKinney) Subramanian & Jain Brachycladium spiciferum, Bainier B. tetramera, (McKinney) Shoemaker Helminthosporium spiciferum, (Bainier) H. tetramerum	Brn1 (GenBank) - article in press Allergens not yet reported

Summary of Comments on Standardized RFI for BMT

Participants in the discussion expressed interest in the following additions/revisions:

Programmatic Information:

- A-2 Total number of unrelated donor transplants (not just matched)
- A-2 Would like to see volume data over a course of years to see trends in activity.
  Inception date important, total volume, + trend in numbers over previous 3-5 years.
- A-4 Consider splitting the 0-5 age group
- Protocol related (C-1 and C-7)
  Would like a yes/no question - Are all patients managed under a protocol (research or standard of care protocol)?
  If patients are done "off-protocol", how is the decision made?
  How many patients are done "off-protocol" and under what circumstances
- Patient selection (C-1)
  Describe process of patient selection for transplantation - how are variances from protocol handled. Is there a Patient Selection Committee, does it meet regularly, who is on it, are minutes kept, etc
  Include what type of HLA match the transplant center requires for allogeneic transplants
- Protocols (C-7)
  The list of protocols should included the research objectives. Could include Protocol Synopses or Executive Summaries.
- Use the UNOS Transplant Administration Survey to provide general facility data.
- Transplant Team (D-1)
  Change wording to number of years physicians have been actively managing transplant patients. Would like to see number of patients actively managed.
  Change wording to 'Current' % of time managing transplant patients.

Outcomes Data Template:

- Length of stay defined as number of days as an inpatient during the course of the transplant.
- Has consideration been given to providing data on disease free survival rather than patient survival (this point was addressed by Horowitz and participants concurred that patient survival would be sufficient)
- Include 3 individual years (e.g. 1999, 2000, 2001); change cumulative to cover same 3 year period.
- Include first three quarters of preceding year for day 100 data (e.g. 2002 through 9/30/02)
- Suggested using 2002 in Kaplan Meier analysis (this point was addressed by Horowitz and participants concurred that is would be too confusing)

Timeline to Release to Payers and Transplant Centers:

Committee to discuss suggested revisions and make revisions as appropriate.	(week of 10/28)
Revised documents to be sent to payers for review and comment.	(week of 11/4)
Additional revisions made as appropriate.	
Document presented to ASBMT Executive Committee at ASH.	(week of 12/2)
Release to payers and transplant centers.	(early 2003)